enabled for their full scope. The Office Action asserts that the specification does not enable *P. haemolytica* vaccines that comprise any mutations in the leukotoxin A, B, C, or D genes or the use of such strains as a vaccine. Applicants respectfully traverse the rejection.

The enablement requirement in the first paragraph of 35 U.S.C. § 112 states that a patent specification must teach a person skilled in the relevant art how to make and use the invention claimed. There are rational limits, however, to the teachings that an enabling specification must provide. First, the specification need not provide knowledge that is generally known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). Second, all that is required to enable a genus claim is that there be a reasonable correlation between the disclosure and the scope of the claim. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970).

The proper standard for determining whether a specification meets the enablement requirement is whether any experimentation that may be needed to practice the claimed invention is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988). Whether a claim is enabled is a question of law based on underlying factual findings. *Wands*, 858 F.2d at 735, 8 U.S.P.Q.2d (BNA) at 1402. Enablement is determined from the viewpoint of persons of skill in the field of the invention at the time the application was filed. *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 U.S.P.Q.2d (BNA) 1332, 1337-38 (Fed. Cir. 2000).

To support a finding of non-enablement, the U.S. Patent and Trademark Office must establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993). The Office must not only explain why it doubts the teachings of the specification, but also must support its

assertions "with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. (BNA) 367, 370 (C.C.P.A. 1971).

Wands sets forth underlying factual inquiries relevant to whether any experimentation that may be needed to practice the claimed invention is undue or unreasonable:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

858 F.2d at 737, 8 U.S.P.Q.2d (BNA) at 1404. In the present application, the weight of evidence, including the teachings of the specification and a declaration of the inventors, favors the conclusion that claims 46-49 and 51-62 are enabled. This evidence is discussed below in connection with each of the *Wands* factors.

Nature of the invention and breadth of the claims (Factors 4 and 8)

Claims 46-49 and 51-62 are directed to vaccines for inducing protective immunity against *P. haemolytica* infection. The vaccines comprise a *P. haemolytica* bacterium comprising a mutation in one of four well-known genes: the leukotoxin C gene (claims 46, 51-53), leukotoxin A (claims 47, 54-56) gene, leukotoxin B gene (claims 48, 57-59), or leukotoxin D gene (claims 49, 60-62). The mutation attenuates the bacterium. Each of the recited genes is part of the leukotoxin operon. The open encodes the leukotoxin protein itself (leukotoxin A) and proteins required for its activation (leukotoxin C) and secretion (leukotoxin B and D). See Cruz *et al.*, *Mol. Microbiol. 4*, 1933-39, 1990, at page 1933, column 1, end of first paragraph. Thus, the leukotoxin B, C, and D genes work in concert to produce a functional leukotoxin A product.

The amount of direction or guidance provided in the specification and the presence or absence of working examples (Factors 2 and 3)

The specification provides a significant amount of direction to those of skill in the art about how to make and use the claimed vaccines. The specification clearly teaches that *P. haemolytica* bacteria with attenuating mutations in the leukotoxin C, A, B, or D genes can be used as vaccines to induce protective immunity against *P. haemolytica* infection, as recited in claims 46-49 and 51-62. The specification teaches that any method known in the art can be used to create the mutations: "[a] mutation is created in the isolated, wild-type DNA region according to any method known in the art. For example, the isolated DNA can be chemically mutagenized, either in a bacterium or *in vitro*. Alternatively, restriction endonucleases can be used to create precise deletions or insertions *in vitro*. Other methods as are known in the art can be used as is desirable for a particular application." Page 7, lines 12-17. In addition, the specification discloses a specific method of site-directed mutagenesis. See page 7, lines 4-17.

The specification teaches that mutant strains of *P. haemolytica*

> can provide the veterinary arts with attenuated, live strains of *P. haemolytica* which are suitable for vaccines to induce protective immunity against *P. haemolytica* infection. For vaccine production, it is desirable that the mutation which attenuates the *P. haemolytica* be an essentially non-reverting mutation. Typically these are deletion or insertion mutations, the latter not being caused by a transposable element. Strains which contain multiple attenuating mutations may also be used, so that the risk of reversion to a wild-type, virulent *P. haemolytica* is vanishingly small.

Paragraph bridging pages 8 and 9. The specification also teaches that, in addition to mutations in the *aroA* and *Pha*IMtase genes, "[o]ther genes in which mutations may be desirable are genes in the leukotoxin operon (C, A, B, D) and neuraminidase." Page 7, lines 11-12.

The specification also teaches how to formulate and administer the claimed vaccines:

> Vaccines are typically formulated using a sterile buffered salt solution. Sucrose and/or gelatin may be used as stabilizers, as is known in the art. It is desirable that the *P. haemolytica* vaccines of the invention be administered by the intranasal or intratracheal route, but subcutaneous, intramuscular, [and] intravenous injections also may be used. Suitable formulations and techniques are taught by Kucera U.S. 4,335,106, Gilmour U.S. 4,346,074, and Berget U.S. 4,957,739. Typically, between 10^7 and 10^{11} CFU are administered per dose, although from 10^5 to 10^3 CFU can be used. Adjuvants also may be added.

Page 9, lines 17-25.

Finally, the specification provides a working example, which demonstrates in detail the construction of a defined *P. haemolytica* mutant (Example 6). The mutant constructed in Example 6 is an *aro*A mutant; however, one of skill in the art would readily have been able to apply this teaching to construction of mutants in the leukotoxin A, B, C, or D genes.

The quantity of experimentation necessary (Factor 1)

The standard for whether a claim is enabled is whether any experimentation that must be carried out is undue. *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). This does not mean that no experimentation at all is permitted. Thus, even if routine experimentation were required to make and use the claimed vaccines as instructed in the specification, that does not make the experimentation undue:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 169 U.S.P.Q. 759 (2d. Cir. 1971), *cert. denied*, 404 U.S. 1018 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. In re Rainer, 52 CCPQ 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re

Colianni, [561 F.2d 220, 195 US.P.Q. 150 (C.C.P.A. 1977)].

Ex parte Jackson, 217 U.S.P.Q. (BNA) 804, 807 (Bd. Pat. App. Interf. 1982).

The state of the prior art and the predictability or unpredictability of the art (Factors 5 and 7)

The nucleotide sequence of the entire *P. haemolytica* leukotoxin operon, including each of the *lkt*A, *lkt*B, *lkt*C, and *lkt*D genes, had long been known in the art when this application was filed. See Figure 3 of Highlander *et al.*, 1989, "DNA Sequence of the *Pasteurella haemolytica* Leukotoxin Gene Cluster," *DNA 8*, 15-28,1989 (Attachment 2 to the amendment filed February 13, 2001). Figure 3 provides both the nucleotide sequence of the operon and the amino acid sequences of the encoded proteins and indicates the location of each of the leukotoxin A, B, C, and D genes.

Methods of making mutations in genes also were known when the present specification was filed. The specification explicitly teaches that "[a] mutation is created in the isolated, wild-type DNA region according to any method known in the art. For example, the isolated DNA can be chemically mutagenized, either in a bacterium or *in vitro*. Alternatively, restriction endonucleases can be used to create precise deletions or insertions *in vitro*. Other methods as are known in the art can be used as is desirable for a particular application." Page 7, lines 12-17.

When the present specification was filed, those of skill in the art also knew how to assay leukotoxin activity and how to detect mutant bacteria in which leukotoxin activity had been lost or altered. See, for example, page 1938 of Cruz *et al.*, 1990. Thus, those of skill in the art knew how to identify which bacteria would be attenuated. Leukotoxin B, C, or D mutations (including mutations in the regulatory regions of the leukotoxin operon) could be detected, for example, by observing altered secretion of leukotoxin protein or altered size of levels of leukotoxin protein.

See Chang *et al.*, "Secretion of the *Pasteurella* leukotoxin by *Escherichia coli*," *FEMS Microbiol. Lett. 60*, 169-74, 1989 (Attachment 1 to the amendment filed February 13, 2001) and Highlander *et al.*, 1989, at page 25.

The level of skill in the art (Factor 6)

The level of skill in the art of vaccine production and bacterial genetics is high. Most of those in the art have Ph.D. degrees. This factor weighs in favor of enablement, especially when taken together with the teachings of the specification and prior art discussed above.

The results of the factual inquiries under *Wands* fully support the legal conclusion that claims 46-49 and 51-62 are enabled. Nonetheless, the U.S. Patent and Trademark Office continues to doubt the enablement provided in the present specification. In particular, the present Office Action faults the specification for "not provid[ing] substantive evidence that the claimed vaccines are capable of inducing protective immunity . . . ." See Paper No. 62 at page 6, second full paragraph, referring to paragraph 9 of Paper No. 62 (the previous Office Action mailed November 13, 2000). The U.S. Patent and Trademark Office has used the wrong standard. The specification need not provide substantive evidence that the claimed vaccines work as described. On the contrary, the U.S. Patent and Trademark Office has the burden of explaining why it doubts the statements in the specification's supporting disclosure and of supporting its assertions "with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370. The Office has not provided evidence or reasoning sufficient to shift to Applicants the burden of rebutting a *prima facie* case that claims 46-49 and 51-62 are not enabled.

The only evidence the Office has proffered to support the enablement rejection is a list of prior art publications that are asserted to show that "vaccines comprising Pasteurella haemolytica

are unpredictable in methods of treating or preventing infection." Paper No. 16, page 11, first full paragraph. The cited documents do not provide the required "acceptable evidence or reasoning" because none of them teaches the type of vaccine disclosed and claimed in the present application, *i.e.*, a vaccine comprising a *P. haemolytica* bacterium comprising an attenuating mutation in a leukotoxin A, B, C, or D gene. In fact, the vaccines disclosed in the cited prior art are quite different from the vaccines recited in the pending claims.

- Weekley & Eyre, *J. Vet. Pharmacol. Therap. 16*, 446-53, 1993, teaches use of the commercial *P. haemolytica* vaccines "Presponse" and "Precon-PH" (page 447, column 1, second full paragraph);

- Confer *et al.*, *Am. J. Vet. Res. 46*, 342-47, 1985, discloses immunization of calves with a commercial *P. haemolytica* / *P. multocida* bacterin or with formalin-killed *P. haemolytica* bacteria (page 342, abstract);

- Conlon & Shewen, *Vaccine 11*, 767-72, 1993, teaches vaccines comprising purified capsular polysaccharide, both alone and in combination with recombinant leuktoxin (page 767, second column, first full paragraph);

- Zeman *et al.*, *J. Vet. Diagn. Invest. 5*, 555-59, 1993, teaches use of an avirulent live culture *P. haemolytica* vaccine (page 557, column 1, lines 1-2);

- Weekley & Eyre, *Res. Commun. Chem. Pathol. Pharmacol. 79*, 389-92, 1993, discloses immunization of rats using live *P. haemolytica* obtained from a commercial vaccine (page 389, abstract);

- Chandrasekaran *et al.*, *Br. Vet. J. 147*, 437-43, 1991, examined the efficacy of "an oil adjuvant vaccine (OAV) incorporating locally isolated strains of *Pasteurella haemolytica* type 7 and *Pasteurella multocida* types A and D (page 437, abstract);

- Chengappa *et al.*, *Vet. Microbiol. 21*, 147-54, 1989, discloses a live vaccine containing both *P. multocida* A:3 and *P. haemolytica* A:1 (page 147, abstract);

- Jericho & Langford, *Can. J. Comp. Med. 46*, 287-92, 1982, teaches vaccination of calves using live *P. haemolytica* in aerosol (page 288);

- Purdy *et al.*, *JAVMA 188*, 589-91, 1986, discloses a live *P. haemolytica* serotype 1 vaccine (page 590, column 1, second full paragraph);

- Corstvet, U.S. Patent 5,256,415, discloses an attenuated strain of *P. haemolytica*

isolated from an asymptomatic calf (abstract); and

- the reviews of Mosier *et al.*, *Res. Vet. Sci. 47*, 1-10, 1989, and Confer, *Vet. Microbiol. 37*, 353-68, 1993, discloses numerous prior art *P. haemolytica* vaccines.

None of the vaccines disclosed in these publications is taught to comprise an attenuating mutation in a leukotoxin A, B, C, or D gene. Thus, the Office's use of these documents to assert that prior art *P. haemolytica* vaccines have limited efficacy or undesired side effects is not at all relevant to whether the present specification enables a vaccine comprising a *P. haemolytica* bacterium comprising an attenuating mutation in a leukotoxin A, B, C, or D gene, as recited in claims 46-49 and 51-62.

Although the Office has not shifted to Applicants the burden of providing rebuttal evidence, Applicants have filed a Declaration of inventors Robert E. Briggs and Fred M. Tatum under 37 C.F.R. § 1.132. See the amendment filed February 13, 2001. The Declaration describes two experiments in which a vaccine comprising a *P. haemolytica* bacterium which comprises a leukotoxin A mutation (a deletion of amino acids 34 to 378) was used to vaccinate calves against *P. haemolytica* infection. This vaccine meets the recitations of claims 47 and 54-56, which recite a vaccine comprising a *P. haemolytica* bacterium that comprises a mutation in a leukotoxin A gene. The Declaration demonstrates that the vaccine provides a protective effect against *P. haemolytica* challenge in the vaccinated calves, both under laboratory and field conditions.

The Office Action dismisses the Declaration because it discusses a strain of *P. haemolytica* not described in the specification and not explicitly recited in the rejected claims (*i.e.*, the strain comprising a deletion of amino acids 34-378 of leukotoxin A). Page 4, paragraph 9. The Office has no legal basis for ignoring the Declaration. The experiments described in the

Declaration demonstrate that a vaccine comprising a *P. haemolytica* bacterium comprising "a mutation in a leukotoxin A gene" works exactly as the specification teaches. This vaccine meets all the limitations of claims 47 and 55-57. Thus, at a minimum the rejection of claims 47 and 55-57 should be withdrawn.

The Office Action also dismisses the Declaration because it "does not address" vaccines comprising a *P. haemolytica* bacterium comprising a mutation in a leukotoxin B, C, or D gene. See Paper No. 19, page 4, paragraph 9. The Declaration, however, is probative of the enablement of such vaccines. All of the genes of the leukotoxin operon function together to produce leukotoxin A protein. Leukotoxin C gene function is required for lytic activity of leukotoxin A, and leukotoxin B and D gene function are required for leukotoxin A secretion. See Cruz *et al.*, 1990, at page 1933, column 1, end of first paragraph. Thus, leukotoxin B, C, and D are all pathway genes leading to the same product (functional leuktoxin A). Because proper functioning of leukotoxin A is dependent on the proper functioning of the leukotoxin B, C, and D genes, a vaccine comprising a *P. haemolytica* bacterium comprising a mutation in any of the leukotoxin B, C, or D genes would be expected to provide protection against *P. haemolytica* challenge.

When correctly analyzed, the weight of the evidence of record in this application favors a finding of enablement of claims 46-49 and 51-62. The scope of the specification's teachings bears a reasonable correlation to the scope of claims 46-49 and 51-62. *In re Fisher*, 427 F.2d at 839, 166 U.S.P.Q. (BNA) at 24. The specification teaches how to make mutations in the four genes recited in claims 46-49 and 51-62, as well as how to prepare and administer the claimed vaccines. A vaccine that falls within the scope of claims 47 and 55-57 works exactly as taught, as demonstrated by the inventors' Declaration. Presented with the teachings of the present

specification, any experimentation required for one of skill in the field of the invention to make and use the claimed vaccines would at most involve routine procedures. Practice of routine procedures is not undue experimentation. *Ex parte Jackson*, 217 U.S.P.Q. (BNA) at 807.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 46-49 and 51-62 Under 35 U.S.C. § 112, first paragraph

Claims 46-49 and 51-62 stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action asserts that the claimed subject matter is not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventors possessed the claimed invention at the time the specification was filed. Applicants respectfully traverse the rejection.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). In determining whether the specification meets the written description requirement for the invention now claimed, "[t]he primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *In re Wertheim,* 541 F.2d 257, 262, 191 U.S.P.Q. (BNA) 90, 96 (C.C.P.A. 1976).

The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). What is required to satisfy the written description requirement depends on the nature of the invention claimed. *In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. (BNA) 592, 593 (C.C.P.A. 1971). Compliance with the written description requirement must be

assessed on a case-by-case basis. *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376, 62 U.S.P.Q.2d (BNA) 1917, 1922 (Fed. Cir. 2002).

The rejected claims recite vaccines for inducing protective immunity against *P. haemolytica* infection. The vaccines comprise a *P. haemolytica* bacterium comprising a mutation in a leukotoxin C gene (claims 46, 51-53), leukotoxin A (claims 47, 54-56) gene, leukotoxin B gene (claims 48, 57-59), or leukotoxin D gene (claims 49, 60-62). The mutation attenuates the bacterium. The specification explicitly describes the use of *P. haemolytica* bacteria with mutations in these genes as vaccines:

> Other genes in which mutations may be desirable are genes in the leukotoxin operon (C, A, B, D) and neuraminidase.
>
> * * *
>
> Such mutants can provide the veterinary arts with attenuated, live strains of *P. haemolytica* which are suitable for vaccines to induce protective immunity against *P. haemolytica* infection. For vaccine production, it is desirable that the mutation which attenuates the *P. haemolytica* be an essentially non-reverting mutation. Typically these are deletion or insertion mutations, the latter not being caused by a transposable element. Strains which contain multiple attenuating mutations may also be used, so that the risk of reversion to a wild-type, virulent *P. haemolytica* is vanishingly small.

Page 7, lines 11-12; paragraph bridging pages 8 and 9.

The Office Action again cites *Fiers v. Revel*, *Amgen v. Chugai*, and *Fiddes v. Baird* to support the written description rejection, asserting that a description of nucleic acids is required. Paper No. 19 at page 9. The cited cases, which address written description of claimed novel genes, are not relevant. Claims 46-49 and 51-62 are not directed to novel genes, but to vaccines comprising a *P. haemolytica* bacterium with a particular characteristic, *i.e.*, a mutation in one of four known genes (leukotoxin A, B, C, or D) that attenuates the bacterium. A specification need

not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). Thus, the present specification need not disclose the sequences of the leukotoxin genes to provide a written description of the claimed vaccines.

In fact, the Office acknowledges that the nucleotide sequence of the entire *P. haemolytica* leukotoxin operon (*i.e.*, the recited leukotoxin A, B, C, and D genes) was known in the art when the specification was filed. Paper No. 19 at page 9, first paragraph, referring to Highlander *et al.*, 1989, "DNA Sequence of the *Pasteurella haemolytica* Leukotoxin Gene Cluster," *DNA 8*, 15-28,1989 (Attachment 2 to the response filed February 13, 2001). The Office dismisses the teachings of Highlander, however, by stating that "Highlander is silent with respect to vaccine compositions that comprise leukotoxin mutations. No suggestion for a Pasteurella haemolytica leukotoxin mutant vaccine strains [sic] could be found in the argued Highlander reference." *Id.* Whether or not Highlander discloses vaccine compositions that comprise leukotoxin mutations, or suggests such strains, has no relevance for whether the present specification sufficiently describes the subject matter of claims 46-49 and 51-62.

The U.S. Patent and Trademark Office also faults the specification for not describing any specific leukotoxin A, B, C, or D mutant strains of *P. haemolytica* that would induce a protective immune response. Paper No. 19 at page 9, second paragraph. None of the claims recites a specific mutant strain. Thus, description of such strains is not required to demonstrate that Applicants possessed the claimed generic invention. See *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1531, 20 U.S.P.Q.2d (BNA) 1300, 1302 (Fed. Cir. 1991) ("Unclaimed subject matter is not subject to the disclosure requirements of § 112").

The specification demonstrates to one of skill in the art that Appellants possessed the

vaccines recited in claims 46-49 and 51-62. *Vas-Cath*, 935 F.2d at 1563-64, 19 U.S.P.Q.2d (BNA) at 1117. Thus, the written description requirement is satisfied. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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